REMARKS

Claims 1-18 are pending in the present application.

The rejection of Claims 1, 5, 7, 8, 12, 13, 15, 17, and 18 under 35 U.S.C. §102(b) over Bruna et al (US 6,488,964) is respectfully traversed.

The Examiner alleges that Bruna et al disclose a tablet comprising 43% gabapentin and 1.7% PEG 6000 in Example 2, which "reads on" a gabapentin granulate comprising polyethylene glycol having a melting point of 50-80 degrees Celsius." Applicants respectfully disagree.

Bruna et al disclose a process for manufacturing coated panicles of GABA analogues. The process entails a coating solution comprising a polymer in an organic solvent is sprayed onto the, *inter alia*, gabapentin particles. In Example 2, which is cited by the Examiner, particles are first aggregated in the presence of a binder (PVP) as described in Example 1 and, then, coated by a spray-coating technique. The coating polymer is described at column 3, lines 57-62 as: polymethacrylate, arninoethyl methacrylate copolymers and cellulose polymers, are alone or in admixture. Accordingly, the coated particles are used in their native native form as sachet or they can be subjected to a tableting process. In Example 2, PEG 6000 acts as lubricant in the tableting process.

At not point is a gabapentin granulate obtained by melt granulating with polyethylene glycol disclosed or suggested by Bruna et al, much less a gabapentin granulate having a melting point comprised between 50 and 80°C as claimed.

Even assuming, *arguendo*, that the aggregation step of Bruna et al can be construed as a granulating process, the aggregation step is conducted in the presence of organic solvents rather than PEG as claimed. Actually, PEG 6000 is absolutely not part of the alleged

conglomerate but it is mixed with the aggregated/coaled particles and, then, reduced into tablets; no melt granulation is disclosed.

Accordingly, Bruna et al fail to anticipate the claimed invention. Withdrawal of this ground of rejection is requested.

The rejections of:

(a) Claims 1, 5, 7, 8, 9, 12, 13, 15, 17, and 18 under 35 U.S.C. §102(b) over Berner et al (WO 03/035040); and

(b) Claims 2, 3, 6, 10, 11, 14, and 16 under 35 U.S.C. §103(a) over Berner et al;

are respectfully traversed.

Berner et al disclose a method of treatment of epilepsy and other disease states which comprises the delivery of gabapentin in a gastric retained dosage form. Berner et al discloses tablets made from a granulate comprising gabapentin, PEG and additives (see, for example, Examples 1-3).

In the Office Action, the Examiner cites Example 3 as describing gastric retained tablets wherein hydrophilic polymers with high swelling capacity such as, for instance, hydroxypropyl methylcellulose and polyethylene oxide provide control of the release of the active ingredient. Example 4 clearly states that "gabapentin formulas were manufactured utilizing a *standard granulation technique*", emphasis added.

However, a standard granulation technique is not melt granulation as required in the claimed invention. Specifically, Applicants submit that "standard granulation" is a term synonymous with "wet granulation" i.e. a process which is carried out in the presence of water. The importance of this difference has already been made apparent in this case in the response and Declaration under 37 C.F.R. §1.132 filed on August 24, 2009.

Specifically, Applicants submit that the claimed invention is not anticipated and/or obvious when the product-by-process limitation ("obtained by *melt* granulating gabapentin with polyethylene glycol") is properly taken into account. With respect to the product-by-process limitations of the presently claimed invention, the courts have enunciated that: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claims is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

There are two important aspects to the *In re Thorpe* standard. First, the products in the "product-by-process" claim must be identical or an obvious variant thereof. Second, patentability of a product may not depend on its method of production, but the method of production cannot be disregarded if that method provides a distinct structure or product. Indeed, the Board and the Courts have said as much, which is set forth in MPEP §2113 in relevant part:

> "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where... the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g. *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)... The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art." (citing *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989)

The foregoing is particularly relevant to the present application, as there are clear differences between the method disclosed by Berner et al and the method of the present invention.

Independent Claims 1 and 12 relate to a gabapentin granulate obtained by melt granulating gabapentin with PEG having a melting point comprised between 50 and 80°C. The present invention is characterized in that PEG is the only granulating agent. This specific granulation method, which is carried out in the absence of granulating liquids, allows to obtain a gabapentin granulate endowed with the required different physical properties compared to a standard gabapentin granulate (wet/alcoholic granulation).

First, it is worth noting that granulate of the invention is substantially free of residual solvents being prepared in the absence of any granulating liquid. Being free of residual solvents is an essential feature of the invention by considering that the presence of said solvents in the granulate is one of the main causes of the degradation of the drug. According to the specification, it has been observed that "by granulating with water, under different experimental conditions and with different procedures, the formation of a hydrate is always obtained, with consequent loss in the original crystalline structure" (see page 2, lines 4-6 of the specification).

On the contrary, in the granulate of the present invention gabapentin keeps its original crystalline form. In addition, when gabapentin is granulated according to the present invention, Applicants do not detect the appearance of gabapentin degradation products, calculated through the amount of the known lactam.

Moreover, granulates obtained by melt granulation have optimum sliding and compressibility physical properties (rest angle 30-35% and Carr index 10-18%). Therefore, the above properties, clearly, indicate distinct characteristic of the final granulate that distinguish the structure of the claimed granulate from a granulate obtained by wet granulation as in Berner et al.

The concept of melt granulation, as well as the absence of solvent as granulating agent, is at least implicitly disclosed in the originally filed application. In fact, inventors themselves located the drawbacks associated with standard granulation with water or industrial granulation with organic solvents (see page 2, lines 3-11). Thus, the technical problem addressed by the present invention is to overcome said drawbacks and, the solution is achieved by a non-standard melt granulation, by avoiding the use of any solvent in the process of the invention.

In addition, experimental work directly and unambiguously discloses the general procedure for the preparation of a granulate according to the invention. Example 1 clearly shows how the mixture containing gabapentin, PEG and, optionally, further additives is heated until the PEG melting point (50-80°C) under stirring and, then, cooled to give the desired stable granulate. No addition of a solvent is required.

To further illustrate that the importance of the process limitation (i.e., melt granulation) Applicants submitted an executed Declaration under 37 C.F.R. §1.132 on August 24, 2009, which shows physical differences obtained by the process of the present invention.

First, Applicants again point out that it is known in the art that gabapentin compositions suffer from stability concerns including, as noted above, loss of the original crystalline form of the active ingredient and toxic lactam formation.
In this regard, Applicants point to paragraph 6 of the Declaration under 37 C.F.R. §1.132, which provides experimental evidences demonstrating that gabapentin maintains its original crystalline form (crystalline Form II) after the melt granulation process of the present invention (see DSC, FT-IR and FT-Raman analysis). In addition, paragraph 7 of the Declaration under 37 C.F.R. §1.132 refers to wet granulation preliminary trials wherein, as

reported in the specification, the formation of a hydrated form of gabapentin has been observed as well as an increase of lactam impurity. In fact, some batches of gabapentin granulate obtained by wet granulation were investigated by FT-Raman analysis; it resulted that all batches prepared contained a different gabapentin polymorphic form i.e. the undesired hydrated one.

Finally, it has been further observed that compositions of the invention are able to maintain the titre of the lactam impurity below 0.2% by weight of gabapentin when subjected to standard stability test (storage conditions of 25°C with 60% of relative humidity and/or of 30°C with 65% of relative humidity) (see paragraph 8 of Declaration under 37 C.F.R. §1.132). Specifically, paragraph 8 of Declaration under 37 C.F.R. §1.132 provides stability date of a specific composition within the scope of the invention, namely:

Gabapentin	88.99%
PEG 4000	4.56%
Starch, pregelatinized	4.45%
Silica, colloidal	0.50%
Magnesium stearate	0.50%

Two batches of the above composition, in a 100 mg and 400 mg capsules formulations, were tested under the above stability conditions. Results in terms of lactam percentage by weight of gabapentin are reported in the following tables:

Batch 154/4 (400mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.4	100.5	101.1	99.4	101.7	100.5
Lactam (% a.i.)	≤ 0.2	0.014	0.021	0.024	0.027	0.034	0.034

Batch 165/4 (100mg)	Specification	Time 0	25°C/60%U.R		30°C/65%U.R.		
			1 month	3 month	1 month	2 month	3 month
Titre (%)	95.5-105.0	99.6	101.6	100.8	101.5	101.3	100.7
Lactam (% a.i.)	≤ 0.2	0.017	0.020	0.022	0.027	0.029	0.032

These data clearly show that the lactam content of the capsules under standard stability conditions does not exceed reference value i.e. 0.2% by weight of gabapentin. In

turn, the above data demonstrates that melt granulating according to the invention allows the preparation of gabapentin pharmaceutical formulations wherein the active ingredient is particularly stable.

In summary, Berner et al fails to anticipate and/or suggest the claimed gabapentin granulate. Indeed, when consideration is given to the method by which the granulate is produced, it is without question that Berner et al cannot affect the patentability of the claimed invention as the melt granulation of the present invention provides clear, distinct structural differences as compared to a granulate prepared by wet granulation as in Berner et al.

In view of the foregoing, withdrawal of these grounds of rejection is requested.

Finally, on page 6 of the Office Action, the Examiner indicates that "Claim 4 would be allowable if rewritten to overcome the rejection (s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action". Applicants respectfully submit that there are no rejections under 35 U.S.C. §112, second paragraph, issued in the outstanding Office Action. Clarification is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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